REMARKS

Claims 1 - 10 were canceled and claims 11-15 were added in a preliminary amendment filed with the application. Claim 14 is canceled above. Claims 11, 12, 13 and 15 are now pending in the application.

In the Office Action of September 27, 2004, claims 11-13 and 15 were rejected under 35 USC §103 as being unpatentable over Borgström *et al.* in view of Ariëns and further in view of Koshino *et al.*

Borgström (Applicant's reference AX) is cited for teaching the use of racemic terbutaline to treat obstructive airway disease, and that only the (-)-terbutaline enantiomer has any agonist activity. Ariëns (Examiner's reference U) is cited for teaching that the inactive enantiomer of drugs may be responsible for undesirable side effects. Koshino (Applicant's reference AR6) is cited for teaching the use of ketotifen in combination with other β-agonist drugs.

Claim 14 having been canceled, applicant believes that the Koshino reference is moot.

The Action concludes that it would be obvious to one of ordinary skill, in light of Borgström and Ariëns, that the use of the *R*-terbutaline enantiomer substantially free of its *S*-enantiomer, for the treatment of inflammatory or obstructive airways disease would avoid, ameliorate or restrict the occurrence of deleterious side effects caused by the *S*-enantiomer. Applicant respectfully disagrees.

Borgström states that "only the (-) [*R*] enantiomer [of terbutaline] exerts the desired pharmacological effects, while the (+)[*S*] enantiomer is devoid of effects in the

pharmacodynamic test models used". Borgström does not teach or even suggest that side effects could be avoided by administering *R*(-)terbutaline substantially free of *S*(+)terbutaline. Although Borgström suggests enhanced potency from administration of (-)-terbutaline, enhanced potency is not the basis of Applicant's invention and such a teaching would not normally motivate the person of skill to remove the therapeutically inactive isomer. To the contrary, as discussed in the present specification, at the time of the present invention, it was the long, widely established and continuing practice to administer β_2 sympathomimetic bronchodilator drugs, such as terbutaline, as a racemic mixture, since it was believed that the "less or inactive enantiomer is devoid of any relevant drug effect and can thus be administered together with the active enantiomer essentially as inactive ballast and without risk to the patient." [specification at page 9, lines 8-17] It is presumably for this reason that, at the time of applicant's filing, virtually all clinical and commercial β-agonists, including terbutaline, were administered only in racemic form.

For the missing teaching of avoiding side effects, the Office relies on Ariëns, who argues the relevancy of chirality in pharmaceuticals and urges that pharmacological studies be undertaken on single enantiomers rather than racemic mixtures. It is important to note that Ariëns was arguing for a position that had not been accepted into the general state of the art. Ariëns was trying to convince pharmacologists to change their views, which were that chiral drugs could be tested as racemates. The instant application is the descendant of an application that was filed (and is entitled to the priority date of) April 5, 1991. In order to avoid hindsight obviousness, it becomes critical to appreciate the state of the art at the time of the invention. It was by no means clear to persons of skill in the art in 1991 that there was a therapeutic advantage to removing the "inert" enantiomer. The Ariëns reference, when viewed by itself, does not necessarily give a complete picture of the art at the time the invention was made. "In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered.....including that which might lead away from the claimed invention."[*In re Dow* 5 USPQ2d 1529, CAFC, 1988]

Consistent with applicant's characterization of the state of the art, Testa and Trager [Chirality 2, 129-133 (1990)], a reference contemporary with applicant's filing date, specifically cites the earlier Ariëns article in the same journal, and cautions against making the assumption that, because enantiomers have differing pharmacology, one should automatically employ pure enantiomers. They state [page 133, last paragraph], "[w]hile it is abundantly clear that a racemic mixture must be considered as the mixture of two pharmacologically distinct entities, it is also clear that this view, in and of itself, does not infer any value judgment. Such judgment awaits the light of scientific fact and it is only in this context that any decision as to develop a racemate or a eutomer as a new drug is convincingly founded." In fact, Testa and Trager created a decision tree to aid in deciding whether to develop a racemic pharmaceutical or a single enantiomer. If it were the case that it would always be obvious to develop a single enantiomer, there would be no need for their decision tree. As they make clear, the mere fact that enantiomers exist is not justification for administering a single enantiomer; even the fact that one of the two enantiomers is more potent is not determinative. Moreover, Testa and Trager provide ample evidence that the outcome of experimentation with racemates and enantiomers is not fully predictable. Examples provided by Testa include (page 131) analogs of clofibric acid, which display reversal in stereoselectivity depending on dose or pharmacokinetic factors; (page 132) carvedilol, in which either racemic or pure S-enantiomer can be preferred depending on the desired therapeutic profile; (page 132) (R)-propranolol, in which the half life of the efficacious R-enantiomer is increased by administration of the racemate rather than the pure enantiomer; and (page 132-133) racemic warfarin in which the R enantiomer inhibits metabolic disposal of the efficacious S-enantiomer thereby presumably improving the half life of the racemate. Even Ariëns own carefully argued thesis outlines eleven possible scenarios for "inactive isomers", and only one of the eleven (202:option 5), describes the case in which the distomer contributes to undesired side effects. An additional copy of Testa and Trager Chirality 2, 129-133 (1990) is included herewith. (It was reference CA in the Supplemental IDS in the parent case.)

In light of the foregoing amendments and remarks, Applicant believes that a *prima facie* case of obviousness has not been made against the now-pending claims. Reconsideration of the rejection is requested.

Respectfully submitted,

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